Remarks

Upon entry of this amendment, claims 1, 2, 13, 14, 16-18, 22, 23, and 34-36 will be pending.

Claims 1, 13, 22, 23, and 34-36 have been amended to more particularly point out and distinctly claim the subject matter, which Applicants regard as the invention.

Specifically, claim 1 has been amended to incorporate Seq ID Nos of the sequences added by the Replacement Sequence Listing filed herewith. Seq ID Nos. 2, 94, and 95, are protein sequences for *C. elegans* SREBP, SCAP, and S2P, respectively. These sequences were incorporated by reference in the application as originally filed on page 44, lines 32-36 and page 64 lines 5-6.

Claim 1 has been further amended to recite that the mis-expression results in a loss-of-function intestinal defect phenotype. Support for the "loss-of-function" feature is found, *inter alia*, at page 7 lines 31-34, page 21 lines 19-29 and 32-33, page 22 lines 17-36, page 23 lines 1-12, page 25 lines 29-35, and page 26 lines 1-2, and in Examples 3, 4, and 5 on pages 44-56.

Claim 13 is amended so that the preamble is consistent with the final step of the claim.

Claim 22 is amended to recite the high stringency hybridization conditions recited as condition no. 8 in Table 1 on page 9 of the application.

Claims 34-36 are amended to render the claims more concise and to include Seq ID Nos.

No new matter is introduced by the amendments to the claims. A marked-up copy of the amended claims is provided in Appendix A. A clean version of the entire set of pending claims is provided in Appendix B. The amendments present the rejected claims in better form for consideration on appeal, and do not introduce any new issues for consideration. Accordingly, entry of the amendment is proper (37 CFR § 1.116).

Amendment to the Specification

Please delete the first paragraph in Example 3 on page 44, line 32 – page 45, line 5, and replace it with the following paragraph:

PCR was carried out on *C. elegans* sequences for SREBP (SEQ ID NO:1) and S2P (SEQ ID NO:95) (Rawson *et al.*, *supra*; GI1559384), and a Genbank sequence (GI3875380), that is annotated as having HMG-CoA reductase homology, and additionally has been determined to have homology to the human SCAP protein. Accordingly, GI3875380 is referred to herein as ceSCAP (SEQ ID NO:94). Fragments of between 0.2kb to 2kb were produced in regions of interest. Primers used for each experiment are shown below. Each primer sequence had at either its 3' or 5' end (as indicated below) the T7 RNA polymerase binding site, ATCGATAATACGACTCACTATAGGG (SEQ ID NO:10), which is designated "T7-" below. The remaining nucleotides in each primer sequence are from ceSREBP (SEQ ID NO:1), ceSCAP (SEQ ID NO:94), or ceS2P (SEQ ID NO:95), respectively.

Remarks

The replacement paragraph differs from the deleted paragraph in that it includes SEQ ID NOs for ceSCAP and ceS2P, which are added with the replacement Sequence Listing filed herewith. A marked-up version of the replacement paragraph is provided as Appendix C.

REPLY

Claim Rejections – 35 USC § 112

New matter rejections

Use of the term "genetically engineered"

In paragraph 5 on page 2 of the office action, the Examiner rejected Claim 1 and all claims that depend therefrom under 35 USC § 112, 1st paragraph, because the recitation of a *C. elegans* that has been "genetically engineered," is considered new matter. Specifically, the Examiner states:

> "Amended claims 1, 2 and newly presented claims 34-36 recite a C.elegans that has been genetically engineered, however, the specification as originally filled does not disclose a C.elegans that has been genetically engineered."

The Examiner's rejection is clearly contrary to the Written Description Guidelines, which state:

> If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

The Examiner supports the rejection by stating that the specification refers to "genetically modified" *C. elegans*, and does not use the term "genetically engineered" *C. elegans*. However, the Examiner makes no argument as to why a skilled artisan would not have understood the inventors to be in possession of the claimed invention at the time of filing. There is clear support for the claimed invention both in the specification as originally filed, and in common usage of the term "genetically engineered". Within the specification as originally filed, applicants direct the Examiner's attention to page 21, lines 1-7, which read:

> "The *in vivo* and *in vitro* models may be genetically engineered or modified so that they 1) have deletions and/or insertions of one or more SREBP pathway genes, 2) harbor interfering RNA sequences derived from SREBP pathway genes, 3) have had one or more endogenous SREBP pathway genes mutated, and/or 4) contain transgenes for mis-expression of wild-type or mutant forms of such genes. Such genetically modified *in vivo* and *in vitro* models are useful for identification of new genes that are involved in the synthesis, activation, control, etc. of SREBP pathway genes and/or gene products."

The Examiner has argued that the passage on page 20, lines 14-17, discloses genetically modified animal models, while the term "genetically engineered" is used for cell lines (in vitro). The above passage makes clear that applicants have used these terms interchangeably. Applicants additionally submit that it is well known in the art that genetic engineering refers to the production of genetic modifications via human intervention. For instance, the commonly used term "genetically modified organisms (GMOs)" refers to genetically engineered crops and other organisms.

For the foregoing reasons, the "new matter" rejection under 35 USC § 112, 1st paragraph, in connection with the term "genetically engineered" is not sustainable and should be withdrawn.

Use of the term "intestinal defect phenotype"

The Examiner also rejected claims 1, 11, 13, and 15, under 35 USC § 112, 1st paragraph, on the grounds that these claims:

> "...recite the term "intestinal defect phenotype", however the specification as originally filed does not disclose the term."

Again, the portion of the Written Description Guidelines recited above makes it clear that the fact that a claim term is not described explicitly in the specification is not proper justification for a new matter rejection. What matters is that the skilled artisan would have understood the inventor(s) to be in possession of the claimed invention at the time of filing. There is ample support for the term "intestinal defect phenotype" in the specification as originally filed such that the skilled artisan would have understood the inventors to be in possession of the claimed invention at the time of filing. The Examiner's attention is particularly drawn to Examples 3, 4, and 5, on pages 44-56, which illustrate the phenotypic result of disrupting ceSREBP, ceS2P, or ceSCAP activity. For instance, the description on page 46 lines 24-31 and page 47 lines 1-3 refers to C. elegans in which ceSREBP has been inactivated by RNAi, and read:

> Their intestine appears paler, or less darkly pigmented, than wild-type, and this is referred to as the "pale intestine" or "Pin" phenotype.
>
> Morphological defects in ceSREBP RNAi larvae (L1 and L2 stages) are confined to the intestine, where ceSREBP appears to be primarily expressed, and specifically affect three cytoplasmic structures in intestinal cells. First, there is a dramatic reduction in the number and average size of pigmented droplets in the intestine. This reduction of pigmented droplets seems to account for the Pin phenotype observed at low magnification.
>
> ...
>
> Second, the gut granules appear larger and more birefringent than in wildtype. Third, many variably sized vesicles appear in the intestine. These vesicles are spherical and transparent; similar vesicles are only rarely observed in wildtype larvae.

Additional intestinal defect phenotypes generated by loss-of-function modification of SREBP pathway proteins are described throughout all lines of pages 47 and 48, page 49 lines 1-15, page 50 lines 7-27, and page 56 lines 1-3.

These intestinal defect phenotypes were reflected in originally filed claims 7 and 11, which read:

7. The animal of Claim 1 wherein said expression or mis-expression of said SREBP pathway protein results in an identifiable phenotype.

11. The animal of Claim 7 wherein said animal is a nematode and said identifiable phenotype is a pale intestine phenotype or other intestinal defect.

Thus the amendment adding the term "intestinal defect phenotype" rephrased and summarized matter that was fully described in the specification and claims as originally filed. As asserted in MPEP 2163.07 (Amendments to Application Which Are Supported in the Original Description), I (Rephrasing):

> Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible. *In re Anderson,* 471 F.2d 1237, 176 USPQ 331 (CCPA 1973).

For the foregoing reasons, the "new matter" rejection under 35 USC § 112, 1st paragraph, in connection with the term "intestinal defect phenotype" is not sustainable and should be withdrawn.

Enablement rejections of genetically-engineered *C. elegans*

Enablement of "transgenic C. elegans"

In item 6 on page 3 of the office action, the Examiner maintained the enablement rejection for reasons of record in the previous office action. In the first full paragraph on page 3 of the office action, the Examiner states that the specification is enabling for "a transgenic C. elegans, ... wherein the endogenous ceSREBP gene of said transgenic C. elegans has been mutated by transposon insertion mutagenesis...". Applicants continue to respectfully decline to use the term "transgenic *C. elegans*" because it in fact does not encompass all the genetically-engineered *C. elegans* of Applicants' invention, and in particular does not encompass all *C. elegans* that has been mutated by transposon insertion mutagenesis according to the methods of this invention. As fully described in Example 5 (TC1 transposon mutagenesis) on pages 50-56, it is the excision of the inserted transposon that generated the characterized loss-of-function mutation. The C. elegans that were identified as having a pale intestine phenotype and a loss of function SREBP mutation no longer carried the TC1 transposon and were therefore were no longer "transgenic".

Disclosure in specification as to the function of ceSREBP

In the paragraph bridging pages 3 and 4 of the office action, the Examiner appears to argue that the specification fails to enable one of ordinary skill in the art to make and use the invention of claim 1 because the precise function of *C. elegans* SREBP, SCAP, and S2P has not been elucidated, specifically whether defects in the ceSREBP affect sterol metabolism or whether they affect fatty acid metabolism. However, the precise function of the SREBP pathway in *C. elegans* need not be fully understood in order for the claimed invention to be useful and enabled. The SREBP pathway is clearly important because of its role in lipid metabolism and because improper lipid metabolism is implicated in a variety of health disorders. It is well known that invertebrate model organisms are useful in the study of evolutionarily conserved genetic pathways, such as the SREBP pathway, and that loss-of-function mutations in a gene provide the means to study the normal function of that gene. Applicants have indicated on page 46, lines 35-36 that the results of experiments that produced a loss-of-function ceSREBP phenotype by RNAi demonstrated "that ceSREBP is required for formation and/or maintenance of lipid droplets in the intestine, the main lipid storage organ of C. elegans." Similarly, the experiments described on page 48 lines 27-36 and page 49 lines 1-15 showed that disruption of endogenous ceS2P (SEQ ID NO 95) and ceSCAP (SEQ ID NO 94) function by RNAi produces similar intestinal and lipid defects and provided evidence that these proteins are likewise required for the formation and/or maintenance of lipid droplets in the intestine. The specification provides ample guidance on how to **make** the genetically-engineered *C. elegans* of claim 1 (see page 20, line 13 – page 28, line 32; and Examples 3-5 on page 44, line 29 – page 56, line 3). The specification provides ample guidance on how to **use** the genetically-engineered *C. elegans*, for example in genetic modifier screens (see page 30 line 25 to page 32, line 27) to identify genes that modify the SREBP pathway, and thus are possible targets for drugs used in the treatment of metabolic disease.

M.P.E.P. § 2164.04, which concerns the burden on the Examiner under the enablement requirement, states:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken

as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

To the extent that the Examiner's rejection is based on the belief that there may be multiple SREBPs, SCAPs and S2Ps in *C. elegans*, the rejection is overcome by the amendment to Claim 1 which incorporates the sequence information for the *C. elegans* SREBP, SCAP and S2P.

Reproducibility and inheritability of intestinal defect phenotype

In the paragraph that begins on page 4 of the office action, the Examiner calls attention to differences in methods for generating the genetically engineered/modified *C. elegans*, and differences in how and whether the changes are inherited, as basis for an enablement rejection. The Examiner has written:

> The next enablement issue is: whether all the methods of creating genetic modification would have produced transgenic nematodes of C. elegans with the same phenotype and whether the changes produced would have been inheritable.

As Applicants explained in response to the first office action inheritability of the intestinal defect phenotype is not needed in order for the genetically engineered worms to have utility in the study of lipid metabolism. Scientists at Exelixis, assignee of the invention, routinely **make** *C. elegans* having knockout of SREBP function induced by RNAi, which results in intestinal defects that are not inheritable beyond first generation progeny. The worms are routinely **used** in Exelixis' Metabolic Disease program. Specifically, the SREBP knockout worms are used in genetic modifier screens, where additional genes are mutated by chemical mutagenesis to identify genes that, when mutated, modify the intestinal defects caused by RNAi-induced knock-out of SREBP function. Genes that modify the SREBP pathway are potential drug targets for metabolic diseases, and can be used to develop assays for high throughput screening of pharmaceutical compounds.

The fact that RNAi does not produce inheritable mutations does not mean that it does not produce consistent phenotypes. Skilled practitioners in the art will recognize that the utility of RNAi is in the ability to rapidly produce consistent phenotypes, and that

these phenotypes are generally not inherited, or are only inherited by the direct progeny of the treated animals. RNAi is widely used to produce specific loss-of-function phenotypes and has been the basis for screens. For further information about how RNAi is used, the Examiner is directed to, for instance, articles by P Gonczy, et al (Nature 2000, 408:331-6) and by CP Hunter (Current Biology 1999, 9:R440-R442). RNAi acts at the level of gene expression and does not produce changes in the genome. However, artisans using the claimed invention could easily and repeatedly perform RNAi experiments, using the methods explained on page 44 lines 32-36, all lines of page 45, and page 46 lines 1-16 of the specification and could expect to obtain the intestinal defect phenotypes described on page 46 line 17-36, all lines of pages 47 and 48, and page 49 lines 1-15. Repeating the RNAi procedure each time it is desired to make C. elegans with the lipid defect phenotypes is routine experimentation. As is implicit from the specification, RNAi acts in a dominant fashion; thus, all or most animals treated by RNAi are expected to display the phenotype associated with reduced activity of the disrupted gene.

In contrast, TC1 transposon mutagenesis and chemical mutagenesis, as disclosed in, respectively, Example 5 and the declaration provided by Cynthia Seidel-Dugan, produced recessive loss-of-function genomic mutations. Accordingly, the mutations are inheritable and produce the associated loss-of-function phenotypes only when homozygous (i.e., both copies of the endogenous gene carry the mutation). It is reiterated that these mutagenesis techniques are widely used in the art and are known to produce inheritable mutations. It is further well known in the art that recessive germline mutations may be propagated through heterozygous animals. In this case, approximately 25% of progeny of such parents will be homozygous according to predictable patterns of Mendelian inheritance. On this subject, the Examiner has written in the paragraph on the middle of page 5 of the office action:

> Regarding the issue of phenotype, applicants have argued that 25% of the heterozygous C. elegans showing the phenotype is in agreement with normal Mendelian segregation. However, as noted above, if the transmission is not germ line transmission, how can one produce C. elegans with the same phenotype again and again every time the assay is repeated.

Applicants wish to correct the Examiner and point out that the 25% of the progeny of heterozygous *C. elegans* show the phenotype. These *C. elegans* are presumed to be homozygous for ceSREBP mutations and thus display the SREBP loss-of-function phenotype.

Also with regard to phenotype, Examiner has written,

> "It is noted the Applicants have provide a declaration that even by chemical mutagenesis they were able to generation a C. elegans that had a pale intestine phenotype, however, it is not clear whether SCAP of S2P mutants would also be produced because the method is not a targeted disruption in a particular gene, rather it is a random mutagenesis."

It is believed that the Examiner may have misinterpreted the experiments described in the declaration and mistakenly understood that the declaration discloses a random mutation that serendipitously produced a pale intestine phenotype. Rather, these methods were used to specifically isolate a genomic mutation in ceSREBP. Applicants call the Examiner's attention to page 3 lines 6-11, of the Seidel-Dugan declaration, which describe that sequence analysis of mutant *C. elegans* confirmed a specific mutation in the ceSREBP gene. Methods for using random chemical mutagenesis to isolate specific mutations are well known in the art and are commonly used by *C. elegans* researchers (for instance, the Examiner is referred to Epstein and Shakes, eds., *Caenorhabditis elegans*: Modern Biological Analysis of an Organism, 1995, (Methods in Cell Biology , Vol 48) and to Ian Hope (ed.), C. elegans: A practical Approach, 2000, The Practical Approach Series). Accordingly, similar techniques could be used to isolate specific mutations in ceSCAP and ceS2P, which would then be confirmed by sequence analysis.

At the beginning of the first full paragraph on page 5, the Examiner stated that Applicants argued in response to the first Office Action, that phenotype uniformity is not required. Applicants' argument was that absolute uniformity is not required. Within the scope of intestinal defect phenotypes, there may be minor phenotypic variations, such as precise appearance of gut granules, presence or absence of larval arrest associated with the intestinal defects, and severity of the pale intestine phenotype. In sum, the shared utility of these models depends on the fact that they have similar phenotypes based on reduced activity of ceSREBP pathway proteins. Amended claim 1 is directed to *C. elegans* that have loss-of-function intestinal defect phenotypes caused by mis-expression

a ceSREBP, ceSCAP, or ceS2P protein, wherein the mis-expression results from genetic engineering or inheritance from a genetically engineered C. elegans. It is further emphasized that the recitation in claim 1 of "genetically engineered" *C. elegans* does not limit the scope of the claim to inheritable modifications nor to genomic alterations. As made clear from the specification, for instance, on page 21 lines 19-29, applicants have included RNAi within the scope of genetic modifications to C. elegans.

In the middle of page 6 of the office action, the Examiner argues that the Applicants have not disclosed what the result of over-expression of an SREBP pathway protein would be. It is believed that the current amendment to Claim 1, which now recites that the mis-expression that results in a loss-of-function intestinal defect phenotype, obviates this aspect of the Examiner's rejections.

Regarding the use of different promoters and selected markers, which the Examiner questioned at the bottom of page 6 of the office action and the beginning of page 7, Applicants have cancelled claims 3, 4, and 6, rendering the objections to these claims moot.

For the foregoing reasons, the specification provides sufficient detail to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. The requirements of 35 U.S.C. § 112, 1st paragraph are satisfied.

Written Description Rejection

In item 7 on page 8 of the office action, the Examiner rejected claims 1-4, 6-11, and 34-36 under 35 U.S.C. §112, 1st paragraph, on the grounds that the claimed invention encompasses *C. elegans* that over-express SREBP pathway proteins which may result in unknown phenotypes. It is believed that the rejection is overcome by the amendment to claim 1 which adds the feature that the mis-expression results in a loss-of-function intestinal defect.

Enablement rejection of polynucleotides

In item 8 on page 9 of the office action, the Examiner rejected claims 22, and 26-28 under 35 U.S.C. for lack of enablement on the grounds that not all of the polynucleotides encompassed by the claim would have the biological activity of SREBP.

In particular, the Examiner has alleged that applicants' recitation of a polypeptide having at least 80% sequence identity to amino acids 1-1113 of ceSREBP (i.e., ceSREBP) allows amino acid changes that alter the activity of the protein. In response, applicants assert that the recitation in Claim 22 of a "functionally active SREBP polypeptide" excludes those mutations that have significantly altered the activity of SREBP. Methods for assessing functional activity of a protein are well known in the art and are described in the specification on page 14 lines 28-36 and page 15 lines 1-13. It is furthermore well known in the art that 80% identity generally represents significant functional conservation. For instance, as demonstrated by the specification and the prior art, the SREBP proteins from mammals, C. elegans, and Drosophila all have similar functions in lipid metabolism. However, as described in the specification on page 42 lines 5-16, even in the most conserved region, the basic Helix-loop-helix domain (approximately amino acid residues 355 to 421 of SEQ ID NO:2), ceSREBP (SEQ ID NO:2) has only approximately 50% identity to the corresponding regions of mouse SREBP-1 (GI 4240012) and Drosophila SREBP (GI079656). Thus, a protein with the much greater homology represented by 80% identity would be expected to have similar activity to ceSREBP. Further, claim 22 is amended to encompass only those polynucleotides that hybridize under high stringency conditions, and thus are expected to be highly related sequences. Claim 22 meets the enablement requirements of 35 U.S.C. § 112, 1st paragraph.

Rejections under 35 USC § 112, second paragraph

Indefiniteness of the term "intestinal defect phenotype"

On page 11 of the office action, the Examiner rejected claims 1-4, 6, 8-11, 13-18, and 34-36, as indefinite because the term "intestinal defect phenotype" is not defined in the specification. However, lack of a definition for a term used in a claim is not an adequate basis for rejection under § 112, second paragraph. The Examiner has not provided any reasoning as to how the use of this term renders the claim indefinite. As indicated in M.P.E.P. § 2173.02:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the

prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The Eaminer's attention is particularly drawn to Examples 3, 4, and 5, on pages 44-56, which provide a detailed description of the intestinal defects that result from disrupting ceSREBP, ceS2P, or ceSCAP activity. The level of skill in the area of *C. elegans* research is high. The researcher of average skill is most certainly able to distinguish a *C. elegans* having intestinal defects from a wild-type *C. elegans*, particularly in light of the specification. Accordingly, the term "intestinal defect phenotype" is sufficiently definite and claim 1 satisfies the requirements of 35 U.S.C. §112, 2nd paragraph.

Indefiniteness of the preamble

In the last paragraph on page 11 of the office action, the Examiner stated that the lack of nexus between the preamble and last step of the claim, renders the claim vague and indefinite. Claim 13 has been amended to obviate this rejection.

CONCLUSION

In view of the claim amendments and for the above reasons, it is believed that all of the rejections are overcome, and that the claims are in condition for allowance.

Respectfully submitted,

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APPENDIX A

1. (Twice Amended) A *C. elegans* that has been genetically engineered to [express or] mis-express an SREBP pathway protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2 (SREBP), SEQ ID NO:94 (SCAP), and SEQ ID NO:95 (S2P), or the progeny of said *C. elegans* that has inherited said [SREBP pathway protein expression or] mis-expression, wherein said [SREBP pathway protein expression or] mis-expression results in [an] a loss-of-function intestinal defect phenotype.

13. (Twice Amended) A method for identifying a gene that modifies the function of a gene encoding an SREBP pathway protein[studying lipid metabolism] comprising obtaining a first *C. elegans* defined by Claim 1 and a second *C elegans* that has the same genetic engineering as the first *C. elegans* and that additionally has a mutation in a gene of interest, and detecting a difference between the intestinal defect phenotype of the first *C. elegans* and the intestinal defect phenotype of the second *C. elegans*, wherein a difference in the phenotypes identifies the gene of interest as capable of modifying the function of the gene encoding said SREBP pathway protein.

22. (Twice Amended) An isolated nucleic acid molecule of less than 15 kb comprising a nucleic acid sequence that (ab) hybridizes to SEQ ID NO:1 under conditions comprising hybridizing in a buffer comprising 6X SSC / [0]25% formamide at [3]42°C and washing in a buffer comprising [2]0.5XSSC at [45]60°C, and (b) encodes a functionally active SREBP polypeptide having at least 80% sequence identity with amino acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2.

23. (Twice Amended) The isolated nucleic acid molecule of Claim 22 that comprises [a nucleic acid sequence having at least 80% sequence identity with nucleotides 1-3419 of SEQ ID NO:1, said identity being determined by using the WU-BLAST-2.0a19 program

and calculating the number of matching identical amino acids divided by the sequence length of] SEQ ID NO:1.

34. (Amended) The *C. elegans* of claim 1 [that has been genetically engineered to express or mis-express] wherein the SREBP pathway protein is SREBP (SEQ ID NO:2).

35. (Amended) The *C. elegans* of claim 1 [that has been genetically engineered to express or mis-express] wherein the SREBP pathway protein is SCAP (SEQ ID NO:94).

36 (Amended) The *C. elegans* of claim 1 [that has been genetically engineered to express or mis-express] wherein the SREBP pathway protein is S2P (SEQ ID NO:95).

APPENDIX B

1. A *C. elegans* that has been genetically engineered to mis-express an SREBP pathway protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2 (SREBP), SEQ ID NO:94 (SCAP), and SEQ ID NO:95 (S2P), or the progeny of said *C. elegans* that has inherited said mis-expression, wherein said mis-expression results in a loss-of-function intestinal defect phenotype.

2. The *C. elegans* of Claim 1 that has been genetically engineered by a method selected from the group consisting of transposon insertion mutagenesis, double-stranded RNA interference, and chemical mutagenesis.

13. A method for identifying a gene that modifies the function of a gene encoding an SREBP pathway protein comprising obtaining a first *C. elegans* defined by Claim 1 and a second *C elegans* that has the same genetic engineering as the first *C. elegans* and that additionally has a mutation in a gene of interest, and detecting a difference between the intestinal defect phenotype of the first *C. elegans* and the intestinal defect phenotype of the second *C. elegans*, wherein a difference in the phenotypes identifies the gene of interest as capable of modifying the function of the gene encoding said SREBP pathway protein.

14. The method of Claim 13 wherein said gene of interest is implicated in cholesterol or fatty acid biosynthesis.

16. The method of Claim 13 wherein said detecting step comprises staining the first and second *C. elegans in vivo* with a fluorescently-labelled fatty acid conjugate to measure lipid content within said first and second *C. elegans*.

17. The method of Claim 16 wherein said fluorescently-labelled fatty acid conjugate comprises a fatty acid selected from the group consisting of 4,4-difluoro-5,7-dimethyl-4-bora-31,41-diaza-s-indacene-3-dodecanoic acid, and 4,4-difluoro-5-methyl-4-bora-3a,4a-diaza-s-indacene-3-dodecanoic acid.

18. A method for studying lipid metabolism comprising administering one or more compounds to a *C. elegans* defined by Claim 1; and observing any changes in lipid content of said *C. elegans*.

22. An isolated nucleic acid molecule of less than 15 kb comprising a nucleic acid sequence that (ab) hybridizes to SEQ ID NO:1 under conditions comprising hybridizing in a buffer comprising 6X SSC / 25% formamide at 42°C and washing in a buffer comprising 0.5XSSC at 60°C, and (b) encodes a functionally active SREBP polypeptide having at least 80% sequence identity with amino acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2.

23. The isolated nucleic acid molecule of Claim 22 that comprises SEQ ID NO:1.

34. The *C. elegans* of claim 1 wherein the SREBP pathway protein is SREBP (SEQ ID NO:2).

35. The *C. elegans* of claim 1 wherein the SREBP pathway protein is SCAP (SEQ ID NO:94).

36. The *C. elegans* of claim 1 wherein the SREBP pathway protein is S2P (SEQ ID NO:95).

APPENDIX C

PCR was carried out on *C. elegans* sequences for SREBP (SEQ ID NO:1) and S2P (SEQ ID NO:95) (Rawson *et al.*, *supra*; GI1559384), and a Genbank sequence (GI3875380), that is annotated as having HMG-CoA reductase homology, and additionally has been determined to have homology to the human SCAP protein. Accordingly, GI3875380 is referred to herein as ceSCAP (SEQ ID NO:94). Fragments of between 0.2kb to 2kb were produced in regions of interest. Primers used for each experiment are shown below. Each primer sequence had at either its 3' or 5' end (as indicated below) the T7 RNA polymerase binding site, ATCGATAATACGACTCACTATAGGG (SEQ ID NO:10), which is designated "T7-" below. The remaining nucleotides in each primer sequence are from ceSREBP (SEQ ID NO:1), ceSCAP (SEQ ID NO:94), or ceS2P (SEQ ID NO:95), respectively